

LETTERS TO THE EDITOR

Validation of the Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) in Single and Multiple Institutions: Limitations and Inferences

We would like to comment on 2 recent studies published in the September 2008 issue of *Biology of Blood and Marrow Transplantation*. Both studies focused on validating the discriminative capacity of the Hematopoietic Cell Transplantation specific-Comorbidity Index (HCT-CI) [1] for outcomes among recipients of allogeneic [2] and autologous [3] HCT.

The first study reviewed comorbidities among patients who were given HLA-matched related HCT (MRD, $n = 184$) or HLA-matched or mismatched umbilical cord blood (UCB, $n = 189$). Numerous conditioning regimens were used that were designated either as nonmyeloablative (NMA, $n = 223$) or myeloablative (MA, $n = 150$). While assessing overall outcomes, patients were also classified into 4 subgroups (MRD-NMA, $n = 96$; MRD-MA, $n = 88$; UCB-NMA, $n = 127$; and UCB-MA, $n = 62$). In the combined cohort, HCT-CI scores of 0, 1, 2, and ≥ 3 predicted both nonrelapse mortality (NRM; 10%, 20%, 24%, and 28%, $P = .01$) and overall survival (OS; 72%, 67%, 51%, and 48%, $P = .01$) at 2 years. Further, in multivariate risk models, the HCT-CI was the only independent prognostic factor for NRM and OS, whereas age, donor source, disease risk, and conditioning type were not. In addition, the distribution of comorbidity scores, as assigned by the HCT-CI, was similar among the 4 subgroups of patients, which validated its sensitivity to detect comorbidities.

Although the overall results confirmed earlier findings by us [1] and others [4-10], including multi-institutional experiences [11,12], that the HCT-CI was a strong predictor of allogeneic HCT outcomes, the authors concluded, based on subgroup analyses, that the HCT-CI did not predict NRM and OS as robustly as had been suggested. Although trends for NRM and OS were seen among 3 of the 4 subgroups, the analyses were limited by the relatively small numbers of patients per group. It is theoretically possible that the HCT-CI may be more discriminatory for some subgroups of patients than for others; however, the most likely explanation for the subgroup findings is

random variation caused by small sample size, as well as the heterogeneity of the patient groups with respect to disease and other risk factors. The performance of other comorbidity indices in these patients might have been informative [13-15]. Uniform failure of all indices to discriminate outcomes consistently among the subgroups would confirm the notion that sample sizes were too small for validation studies.

In comparison, the concurrently published Ottawa study, despite a relatively small sample size ($N = 126$), had the advantage of a homogeneous patient population. All patients had a single diagnosis, multiple myeloma (MM), received autologous HCT, and were given a single conditioning regimen. Further, the authors compared the performance of the HCT-CI to another comorbidity index, described by Charlson, which strengthened their conclusion that indices specifically designed to assess comorbidities in the setting of HCT could provide accurate information about HCT-related toxicities and help decision making.

However, the finding that lung, liver, and renal comorbidities were equally well captured by HCT-CI and the CCI was surprising [1,4]. The HCT-CI was designed to be more sensitive in grading those comorbidities by including laboratory tests, whereas the CCI relied on clinical findings. Lack of information on laboratory data in many patients, for example, 49% of patients did not have pulmonary function assessment, might have downgraded the sensitivity of the HCT-CI and, hence, masked the true distribution of comorbidities in the overall cohort.

We agree that validation of the HCT-CI in different institutions and across a broad range of transplant conditions is important. This validation must take into account appropriate sample sizes, adequate numbers of tested events, accurate scoring methodology, and the use of other comorbidity indices for comparison. Our ongoing efforts are focused on such validation, both retrospectively and prospectively, among large cohorts of patients from different institutions. Large sample sizes will allow for robust subset analyses and appropriate adjustment of confounding factors needed to confirm the validity and generalizability of the HCT-CI. In the meantime, we believe that comorbidity evaluation should be a vital part of pretransplant assessment and decision making.

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Donor CMV Serostatus Not Predictive of Relapse in D-/R-Pediatric HCT

To the Editor:

Cytomegalovirus (CMV) remains a major cause of complications in hematopoietic cell transplantation (HCT). Recipient CMV serostatus remains a predictor of non-relapse mortality in the ganciclovir era and seronegative recipients with a seronegative donor

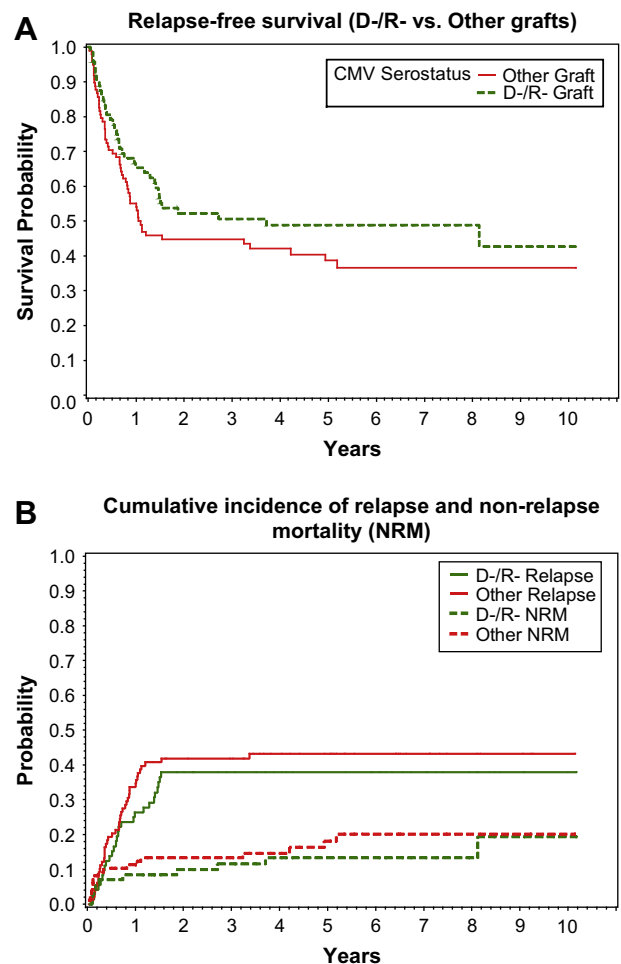


Figure 1. Panel A: relapse-free survival (log-rank $p = 0.16$). **Panel B:** cumulative incidence of relapse and non-relapse mortality (log-rank $p = 0.29$ and $p = 0.98$, respectively).